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History.—J., a man aged 45, Swedish, a sheet-metal worker, entered the Peter Bent Brigham Hospital, Sept. 11, 1913, complaining of chills, fever and bloody urine. The family history was unimportant as related to the present illness. The patient had interstitial keratitis at 3 years (?), and measles and small-pox as a child, but no other infectious diseases in childhood. The patient came to the United States nineteen years ago and served in the Navy during the Spanish-American War. He has been a sailor for several years since, usually serving as engineer on a private yacht. Patient has not been south of New York for twelve years. Ten years ago he had an attack of pneumonia; there was no residue. Four years ago in September, patient had a sudden chill, followed in one hour by fever and sweating. Following this attack, he passed dark urine for from six to eight hours. The next day he felt perfectly well. He had no more attacks that year. During the following fall and winter there were five or six attacks of a similar nature, and two years ago and last year patient had four or five attacks similar in every respect to those previously experienced. These attacks always followed some slight exposure to dampness or cold. He would have a chilly sensation, his legs would become numb and cold, and then a shaking chill would follow. These chills varied in intensity. With each attack he passed dark urine. In the spring of 1913 he experienced another attack. Quinin has been taken in large doses but produces no effect. Patient denies lues. His habits were unimportant.

Present Illness.—September 10, at 9 a. m., patient was standing on the street and felt chilly. At 10 a. m. an attack similar in all respects to the preceding started with a chill, followed by fever and sweating at 11 a. m. with the passing of dark urine.

Physical Examination.—This shows a well built white man, lying quietly in bed. The pupils of the eyes are irregular,

being the shape of apple-seed. The lower iris appears to be drawn into a scar. The corneas are cloudy. The teeth are in good condition. The throat is negative. There is no general enlargement of the lymph-nodes. The chest and lungs are negative. Both heart-sounds are heard and normal; there are no murmurs. The pulse is of good quality, regular and normal. The systolic blood-pressure is 118, diastolic 68. The abdomen is negative; spleen is not palpable; liver shows no enlargement; there are no masses and no tenderness. The extremities show no scars or edema. The deep and superficial reflexes are elicited and found normal.

Clinical Findings.—Blood: Hemoglobin (Sahli), 90 per cent.; white blood-cells, 8,600; no malarial parasites; differential count, normal; platelets, 400,000 per cubic millimeter. The stool contains no blood or parasitic ova, and is essentially negative. The urine is amber, clear and shows no albumin, blood or casts. The Wassermann reaction (blood-serum) is positive.

Course.—September 15: Patient had an attack of chills followed by fever and sweating. No malarial parasites are found. Urine is port wine color and contains much albumin and many pigment casts, but no blood. Spectroscope shows bands of oxyhemoglobin.

September 16: Patient's feet were soaked in ice-water for twenty minutes. One hour later hemoglobin was demonstrated in the urine. There was no chill or fever.

September 17: Neosalvarsan, 0.6 gm., was administered intravenously.

September 18: Wassermann reaction (blood-serum) was positive.

September 23: Patient had one of his attacks at 9 a. m.

September 24: Neosalvarsan, 0.6 gm., was administered intravenously.

September 25: Wassermann (blood-serum) was positive.

September 28: Patient had another attack, much less severe. There was no chill and no fever.

September 29: The feet were soaked in ice-water twenty minutes. Urine exhibited hemoglobin. Patient was discharged to return at intervals for treatment.

October 2: Salvarsan, 0.4 gm., was administered intravenously.

October 16: Salvarsan, 0.4 gm., was administered intravenously.

October 24: Patient reported a paroxysm, less severe than former one.

November 12: Salvarsan, 0.4 gm., was administered intravenously.

The patient is now on intramuscular injections of salicylate of mercury.

Additional Data.—Just after the onset of an attack the patient's blood was drawn from the median basilic vein. On centrifugalizing the serum was deeply tinged with red and showed the characteristic bands of oxyhemoglobin with the spectroscope, thus demonstrating an actual hemoglobinemia.

During an attack the patient's blood was drawn into citrate-salt solution to prevent clotting. The corpuscles were then centrifuged and washed. These were suspended in various strengths of salt solution paralleled by control in order to determine the presence of pathologic fragility; with the result which is tabulated.

The conclusion was drawn that there probably existed no very definite pathologic fragility in the cellular elements of the blood.

Donath and Landsteiner,[1] in 1906, studied a case of paroxysmal hemoglobinuria and found that they could reproduce *in vitro* what had occurred *in vivo*. They

TEST FOR PATHOLOGIC FRAGILITY

Time	Patient's Corpuscles Percentage Salt Solution						Control Corpuscles Percentage Salt Solution					
	0.7	0.6	0.5	0.4	0.3	0.2	0.7	0.6	0.5	0.4	0.3	0.2
Started...	0.7	0.6	0.5	0.4	0.3	0.2	0.7	0.6	0.5	0.4	0.3	0.2
4:10	0	0	0	0	0	*	0	0	0	0	0	*
4:20	0	0	0	0	0	+	0	0	0	0	0	+
4:30	0	0	0	0	†	+	0	0	0	0	†	+
5:00	0	0	0	0	+	+	0	0	0	0	+	+
6:00	0	0	0	0	+	+	0	0	0	0	+	+

* Hemolysis.
† Partial hemolysis.

found that they could hemolyze the patient's corpuscles with the patient's serum when the two in contact were cooled to 0 C. (32 F.) for half an hour and subsequently incubated at 37 C. (98.6 F.) for three hours. Cooke,[2] in a series of exhaustive experiments, found the same true of his patient. He modified the original Landsteiner technic as follows: Instead of the subsequent incubation for three hours, he found that by careful heating over a burner he could obtain hemolysis with subsequent incubation for half an hour. The blood of the patient, J., was taken from the median vein and caught in citrate-salt solution (1 part of solution to 4 of blood) and treated as follows:

1. Donath and Landsteiner: Ztschr. f. klin. Med., 1906, No. 58, p. 173.
2. Cooke: Am. Jour. Med. Sc., August, 1912, p. 203.

PATIENT'S BLOOD

Cooled to 0 C. for half an hour. No hemolysis.

Heated and incubated at 37 C. for half an hour. No hemolysis.

Cooled to 0 C. for half an hour and heated and incubated at 37 C. for half an hour. Hemolysis almost complete (whole blood).

Patient's washed corpuscles (suspended in normal salt solution) cooled to 0 C. for half an hour and heated and incubated at 37 C. for half an hour. No hemolysis.

CONTROL BLOOD

Cooled to 0 C. for half an hour. No hemolysis.

Heated and incubated at 37 C. for half an hour. No hemolysis.

Cooled to 0 C. for half an hour and heated and incubated at 37 C. for half an hour. No hemolysis.

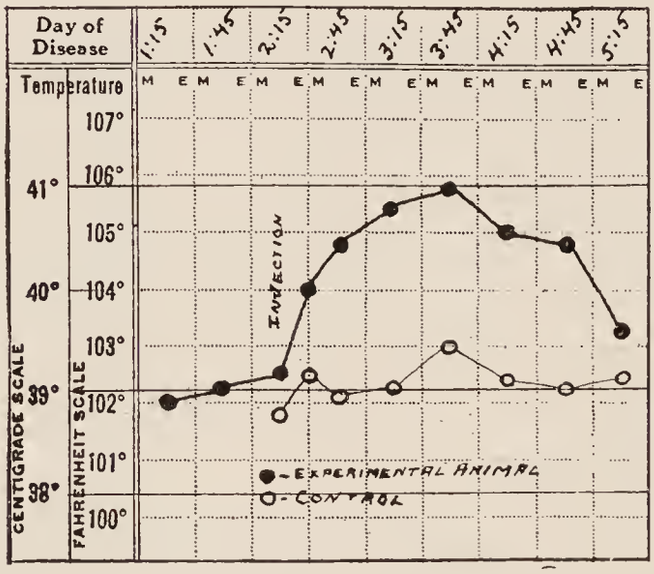

Chart 1.—Temperature curves of rabbit injected with oxyhemoglobin and of control rabbit injected with salt solution.

We also found, as others before had found, that the patient's serum would hemolyze the corpuscles from another person, while the serum of the other person would not hemolyze the patient's corpuscles.

PATIENT'S SERUM AGAINST CONTROL'S WASHED CORPUSCLES

Washed corpuscles, cooled to 0 C. for half an hour and heated and incubated at 37 C. for half an hour. Hemolysis complete.

CONTROL'S SERUM AGAINST PATIENT'S WASHED CORPUSCLES

Washed corpuscles cooled to 0 C. for half an hour and heated and incubated at 37 C. for half an hour. No hemolysis.

No attempt was made to do this quantitatively but merely to establish this case as a clinical entity by using the reaction diagnostically.

The occurrence of paroxysms of hemoglobinuria, the absence of malarial organisms, the increase in blood platelets, the hemoglobinuria after cooling the extremities, and finally the demonstration in the blood of an autohemolysin without increased corpuscular fragility seem to warrant the diagnosis of paroxysmal hemoglobinuria, so-called.

As to the nature of the autohemolysin, Cooke,[2] in his most admirable work, established the following in his case. 1. An autohemolysin exists. 2. The reaction follows the Ehrlich theory of complement—antibody-cell combination. 3. The mode of action is as follows:

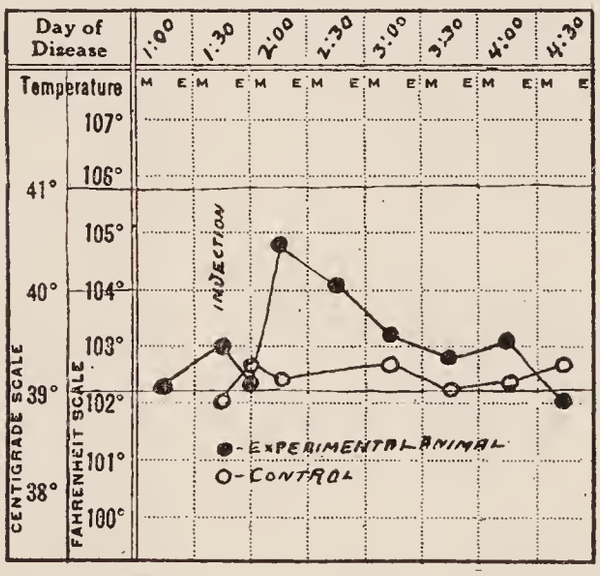

Chart 2.—Temperature curves of rabbit injected with oxyhemoglobin and control receiving no injection.

The antibody may be taken up from inactive serum (patient's) in the cold, the combination with the corpuscles being rather unstable; complement is absorbed from active serum together with antibody in the cold; complement unites with antibody only under the influence of cold; red blood-cells exposed to inactive serum are more or less resistant to hemolysis on account of complementoid present. He concludes that antibody unites with corpuscle and complement with antibody only under the influence of cold, the lytic action being exhibited on subsequent elevation of temperature.

SYMPTOMATOLOGY

The paroxysms exhibited by our patient resemble in almost every respect those seen in malarial infections. Browne,[3] in experiments on rabbits, was able to produce paroxysms resembling those seen in malarial infection by injections of hematin intravenously. Inasmuch as the paroxysms of the hemoglobinuric so closely resembled malaria, it was thought that perhaps here, too, the phenomena were due to the releasing of blood pigment into the menstruum. To test this theory, several rabbits were injected intravenously with hemoglobin. Enough rabbit's blood was drawn to give about 1.5 c.c. of corpuscles. The blood was defibrinated, centrifuged, and the corpuscles laked with sterile distilled water and made up with sterile salt solution. This was controlled

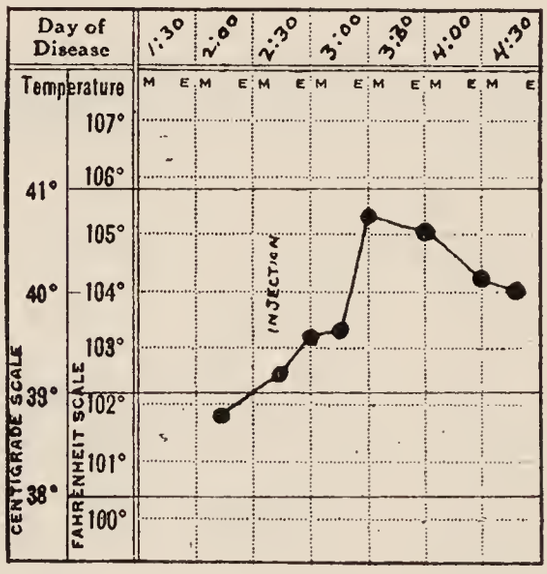

Chart 3.—Temperature curve of rabbit injected with oxyhemoglobin. No control.

by examination with the spectroscope, and was used for injection. The controls received injections of normal salt solution. No attempt at dosage was made, but this amount was taken arbitrarily.

The reaction produced was as follows: The animal when first injected was restless, soon becoming droopy, crouching in a corner with its ears back and hair erect. The vessels of the ears were constricted and the ears cold. This lasted for from fifteen minutes to half an hour and was followed by a period when the peripheral vessels were dilated and the ears warm. The temperature began to rise immediately after injection and

3. Browne: Jour. Exper. Med., 1912, xv, 579.

reached a maximum in from half an hour to one hour, the elevation lasting for irregular periods. This is shown in the accompanying charts. Some animals reacted better than others. In no instance, even on increasing the dosage greatly, could anything simulating the shaking chill be produced. It seems suggestive, though not conclusive, that the loosing of hemoglobin into the blood-stream produces the reaction seen in hemoglobinurics and not the factor, whatever it may be, which causes the hemolysis. The fate of the hemoglobin after injection cannot be determined. It may perhaps undergo some change in the body before producing the reaction.

ETIOLOGY

Cooke[2] states that, since the introduction of the Wassermann reaction, 90 per cent. of hemoglobinurics give a positive reaction. Previous to that time a history or stigmata of lues could be obtained in many instances. Barrett and Yorke[4] state that they could find in the blood of persons infected with organisms of malarial fever no such autohemolysin as has been demonstrated in the serum of the hemoglobinuric. Landsteiner[1] found in six out of sixty-five cases of general paresis that the blood of the individual contained an autohemolysin giving the reaction seen in hemglobinurics. Several patients with syphilitic involvement of the central nervous system, including tabes and cerebrospinal syphilis, were examined here and some found to possess in their blood-serum an autohemolysin. When such a person had his feet soaked in ice-water for twenty minutes, no hemoglobinuria resulted. This suggested the possibility that the hemoglobinuric might possess a kidney with an increased permeability; witness the albumin and casts at the time of a paroxysm. To determine this point, the various renal function tests were tried.

In the case of J., phenolsulphonephthalein (1 c.c. standard solution given intramuscularly) resulted in an excretion of 55 per cent. the first hour, and a total excretion the second hour of 80 per cent.

The total amount of potassium iodid, 10 gm., was excreted in forty-eight hours.

The sodium chlorid output on the "house diet" (from 7 to 9 gm. of sodium chlorid) was 7.4 gm.; plus 10 gm.

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4. Barrett and Yorke: Am. Jour. Trop. Med. and Hyg., 1909, iii, 152.

of sodium chlorid, it was 16.4 gm. the first day, 14.7 gm. the second day, and 10.6 gm. the third day.

The total nitrogen output on the "house diet" was 15.9 gm.; plus 20 gm. of urea it was 26.8 gm. the first day and 18.5 gm. the second day.

The phenolsulphonephthalein and potassium iodid were certainly put out in excess of normal, whereas the salt and nitrogen were at the upper limit of normal. It is suggestive though we can draw no definite conclusions from one case, of a certain degree of hyperpermeability.

On the whole, a luetic rather than a malarial origin seems the more plausible in view of our present knowledge.

TREATMENT

Pringsheim,[5] by the intramuscular injection of cholesterin emulsions was able to hold the paroxysms in abeyance in one patient. Unfortunately, he lost sight of his patient and could not follow up his admirable start. In the case of J., addition of cholesterin to the serum *in vitro* inhibited the hemolysin exhibited by the control without cholesterin, owing probably to its anticomplementary properties. A vigorous antisyphilitic regimen seems the much more plausible course in view of the positive Wassermann. This was undertaken in the case of J. No case heretofore has been followed up to the point at which the Wassermann has become negative. At present, the Wassermann in this case is positive, though titration shows it to be weaker than at the first examination. The paroxysms have grown progressively less frequent and less severe. The case, however, will have to be followed up to the point of the Wassermann's becoming negative.

SUMMARY

We have before us a patient in whose blood-serum, either constantly to act on exposure to cold or else brought into existence by cold, exists a substance which hemolyzes the red blood-cells. This gives rise to a hemoglobinemia which in turn provokes the phenomena of a paroxysm very much like that provoked by the loosing of hematin by the action of the malarial parasite. The excretion of the hemoglobin in the urine by

5. Pringsheim: München. med. Wchnschr., 1912, p. 1757.

the kidneys is one of the most striking of the phenomena and gives the disease its name. This autohemolytic substance in the blood is in all probability the result of infection by the *Spirochaeta pallida*. On the other hand, the possibility exists that the same substance which is produced by the organism of syphilis and to which we give the name antibody and which produces fixation of complement, thus giving a positive Wassermann, is produced by some other agency in the disease under discussion. Thus there may exist a positive Wassermann without syphilis. The existence of this same substance, which gives rise to hemolysis, in parasyphilitics, so-called, makes it highly probable that the etiologic factor here, too, is syphilis. It is quite possible that hemolysis may take place in the menstruum of the parasyphilitic and that it is an increased permeability in the hemoglobinuric which gives rise to actual hemoglobinuria.

It remains to be seen whether or not specific treatment will help clear up the difficulty of etiology, and this I shall report later.

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